Dexmedetomidine-Grand Rounds

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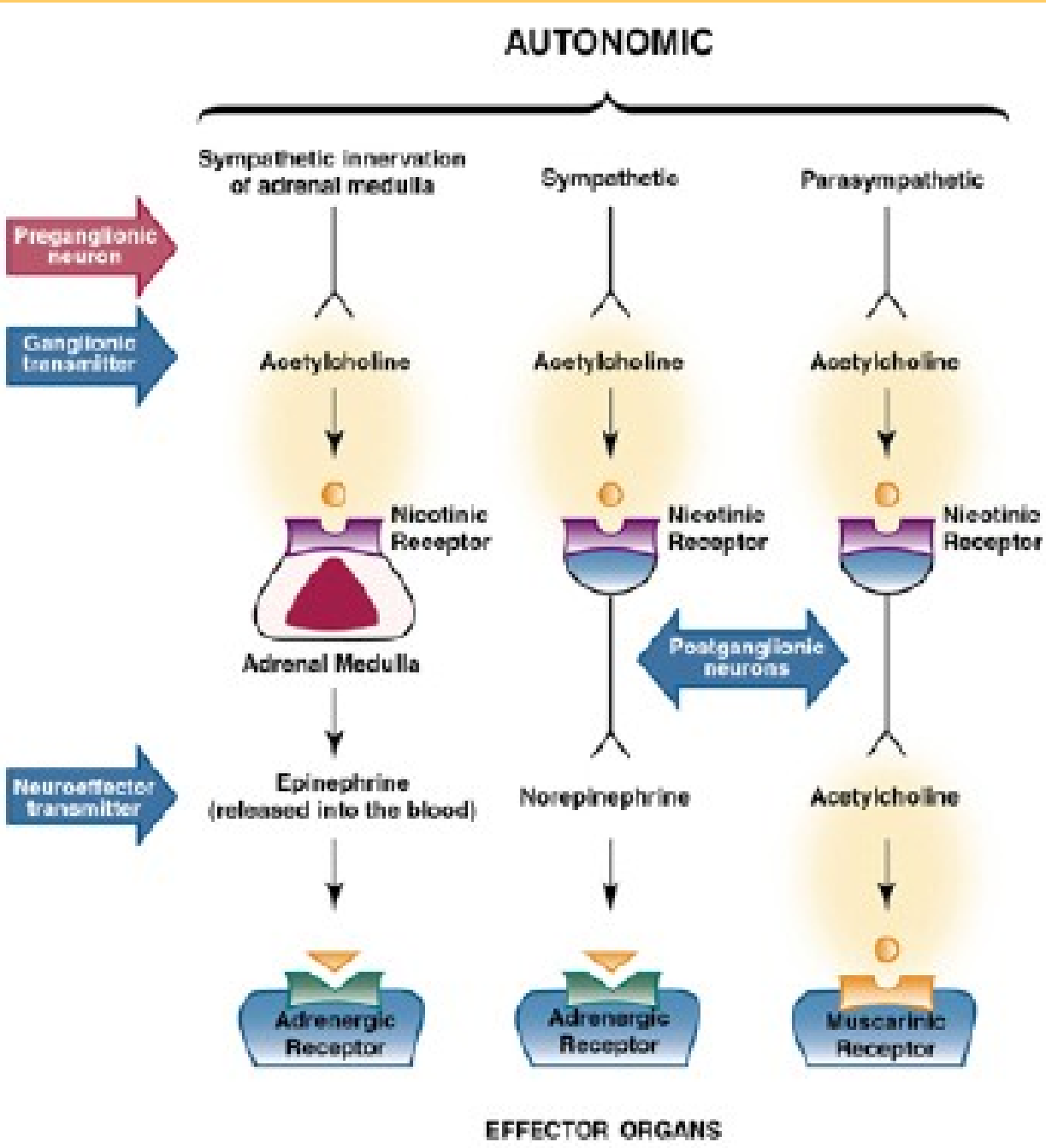
  - National Capital Consortium
  - Spring 2005

Dexmedetomidine

- Overview, including Pharmacology
- Clinical Uses
  - ICU
  - Neuro
  - General OR
  - Cardiothoracic/Major Vascular
  - Regional
  - OB
  - Pain
  - Pediatrics

Dexmedetomidine

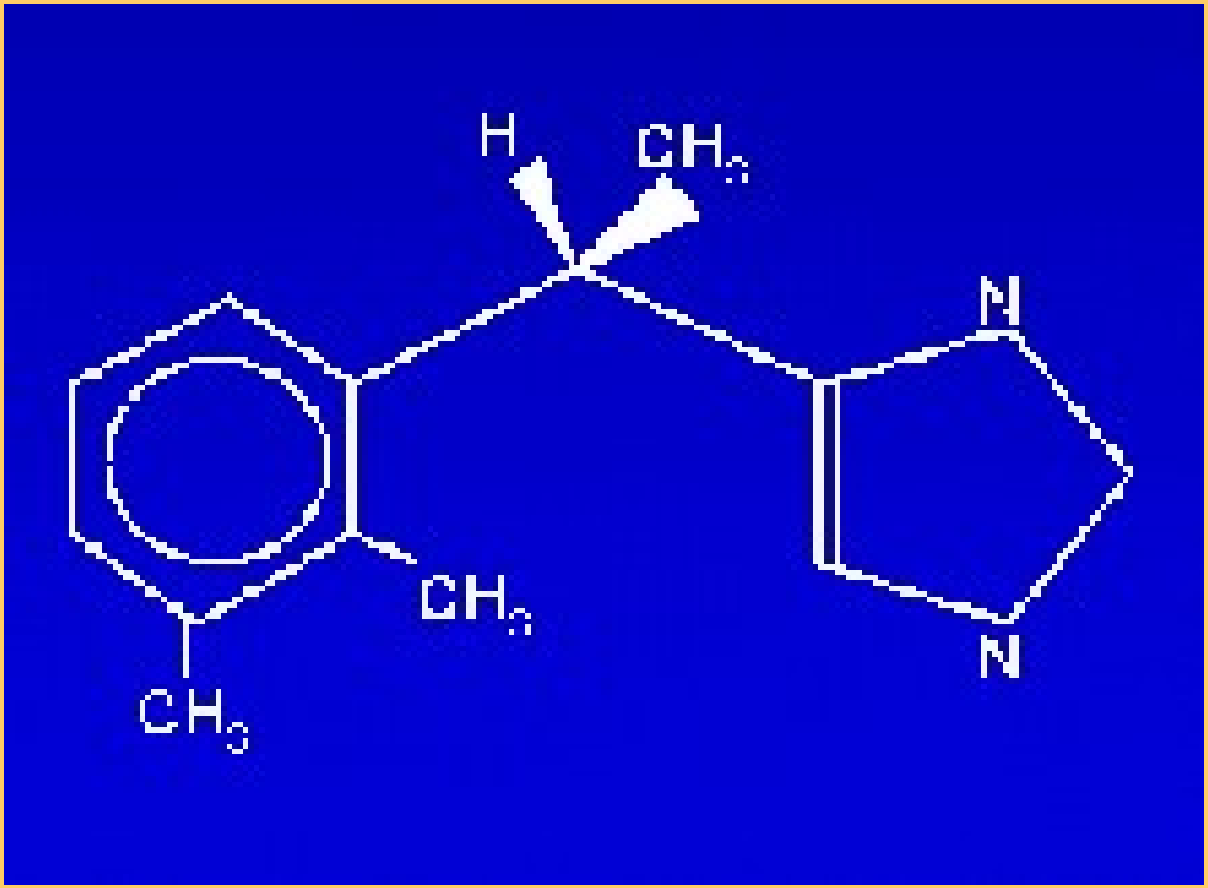
- Overview
  - ANS
    - Alpha2 Receptors
      - Central Receptors
      - Peripheral Receptors
- Pharmacology
      - Metabolism
      - Elimination
      - Pharmacokinetics
- Side Effects
- Dosing


AUTONOMIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
Nicotinic Receptor
Nicotinic Receptor
Nicotinic Receptor
Adrenal Medulla
Postganglionic neurons
Neuroeffector transmitter
Epinephrine (released into the blood)
Norepinephrine
Acetylcholine
Adrenergic Receptor
Adrenergic Receptor
Muscarinic Receptor
EFFECTOR ORGANS

Adrenergic receptors

α_1	α_2
Smooth Muscle	Pre-synaptic
Constriction	**Inhibits NE Release**

Dexmedetomidine



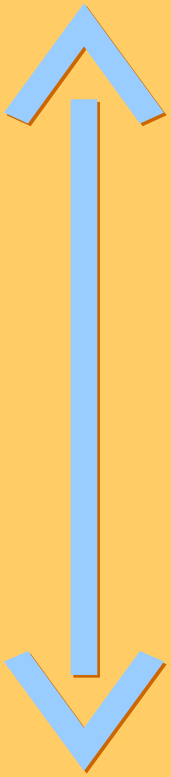
Alpha2 Selectivity

- **Dexmedetomidine selectively acts on alpha$_2$-adrenergic receptors**

Drug	α_2/α_1 selectivity
Dexmedetomidine	1,600
Clonidine	220

Alpha-Adrenoceptor Agonists

Alpha 1



Alpha 2

- Norepinephrine
- Epinephrine
- Dopamine
- Tizanidine
- Clonidine
- Mivazerol
- Guanfacine
- Guanabenz
- Medetomidine
- Dexmedetomidine

Site Of Activity

- Receptors located centrally or peripherally
  - Centrally
    - CNS
      - Brain (locus ceruleus)
    - Spinal cord
    - Autonomic nerves
    - Cardiac
    - Pulmonary
    - Renal
  - Peripheral
    - Vascular
    - Coronary

Central Receptor Effects

- CNS
  - Sedation
  - Anxiolysis
  - Amnesia
- Spinal
  - Analgesia
- Autonomic Nerves
  - Decreased Catecholamine Release

Central Receptor Effects

- Cardiovascular
  - Hypotension and Bradycardia
  - Hypertension
  - Decreased myocardial oxygen consumption
    - *Lawrence et al. The effect of dexmedetomidine on the balance of myocardial energy requirements and oxygen supply and demand. Anesth Analg. 1996;82:544-550.*
- Respiratory
  - Bronchodilation
  - Absence of Respiratory Depression
- Renal
  - Promotion of Diuresis

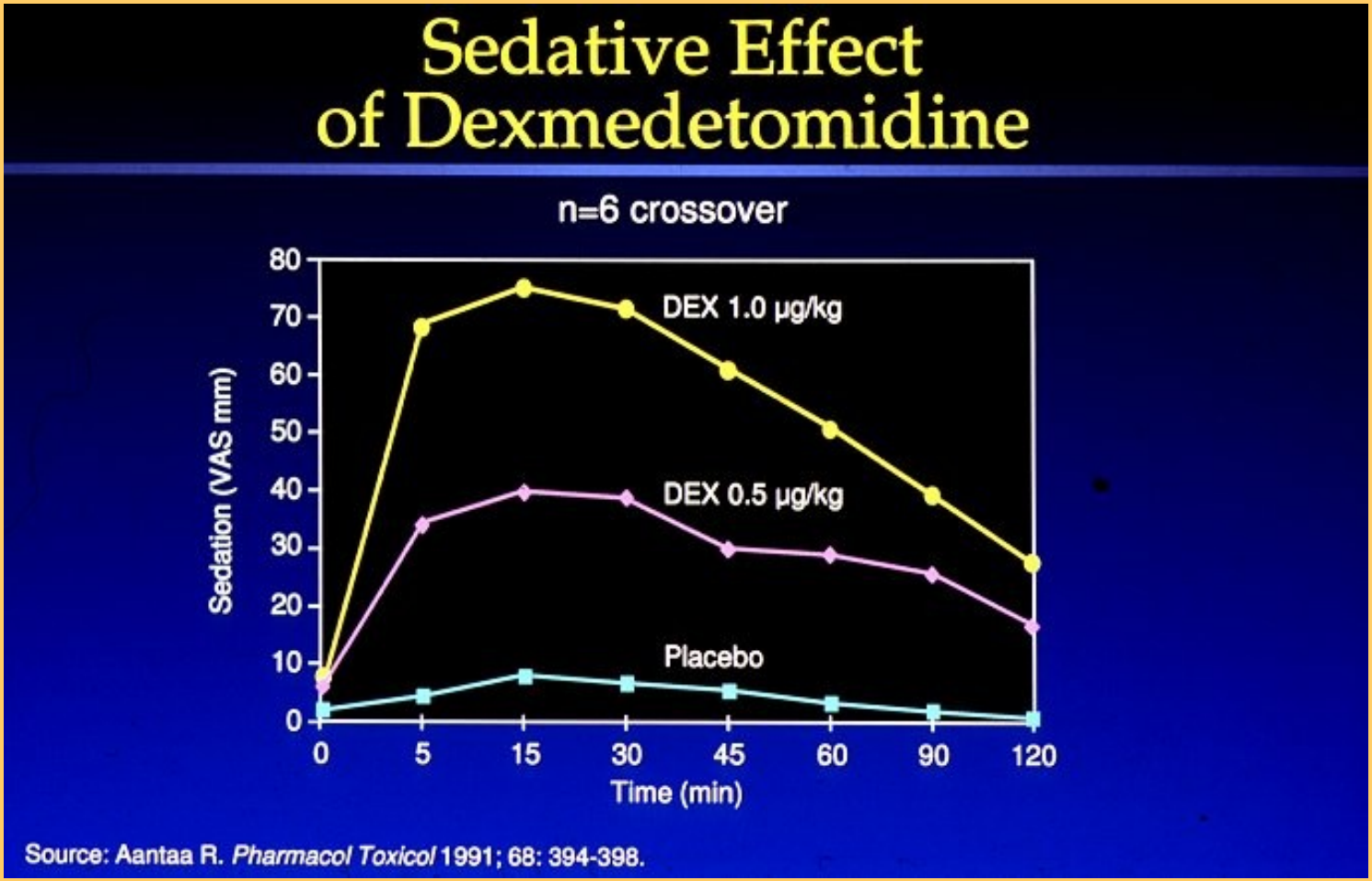
Central Receptor Effects

- Endocrine
  - Decreased
    - insulin release
    - cortisol release
- Gastrointestinal
  - Decreased salivation

Central CNS Effects

- Sedation/Anxiolysis
  - Dose dependent
  - Minimal respiratory depression
  - Arousable and cooperative
  - Reversible with antagonist
    - Atipamezole
- Mimics natural sleep while permitting arousal
  - *Nelson et al. The alpha2 agonist dexmedetomidine converges on an endogenous sleep promoting pathway to exert its sedative effects. Anesthesiology. 2003; 98:428-436*

Central CNS Effects



Central CNS Effects

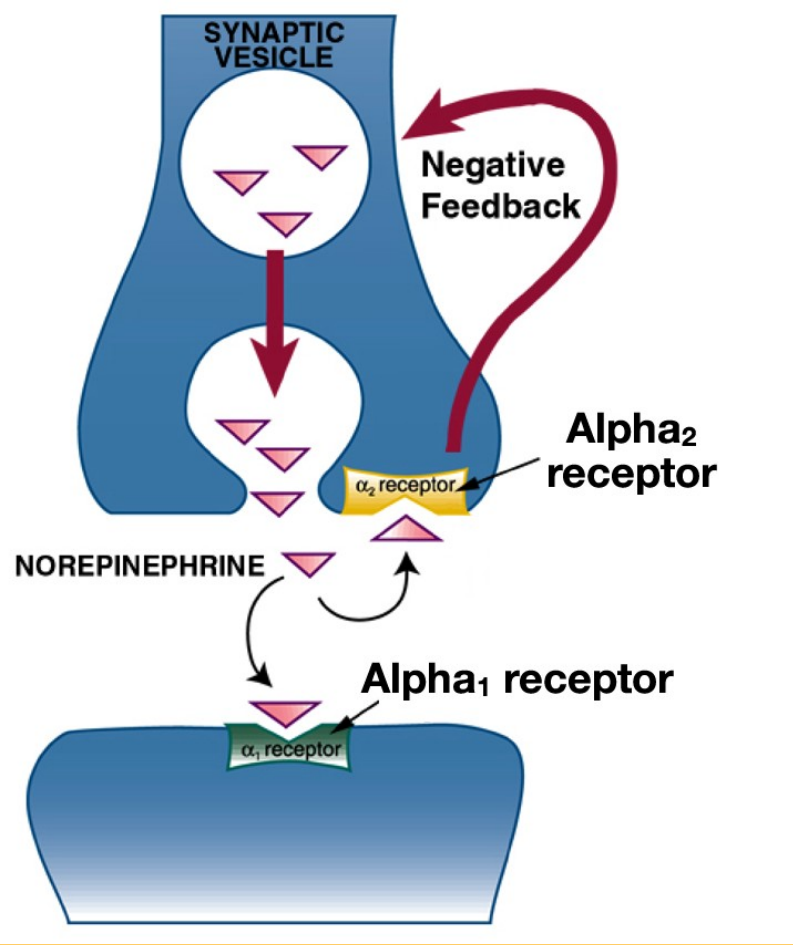
- Amnesia
  - Incomplete with 50% reduction in recall.

Central Spinal Effect

- Analgesia
  - Spinal cord, dorsal horn

Central Autonomic Effects

- Adrenergic receptors
  - Modulate sympathetic response “negative feedback loop”
    - Alpha2 binding inhibits further sympathatic outflow
  - Regulate release of neurotransmitters
  - Control epinephrine, norepinephrine release



Central Autonomic Effects

- Presynaptic Autonomic Nerves
  - Decreased Catecholamine Release by negative inhibition
    - Plasma Epi and NE diminished by 72%
      - *Talke et al. The hemodynamic and adrenergic effects of perioperative Dexmedetomidine infusion after vascular surgery. Anesth Analg. 2000;90:834-839.*
      - *Talke et al. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. Anesth Analg. 1997;85:1136-1142.*

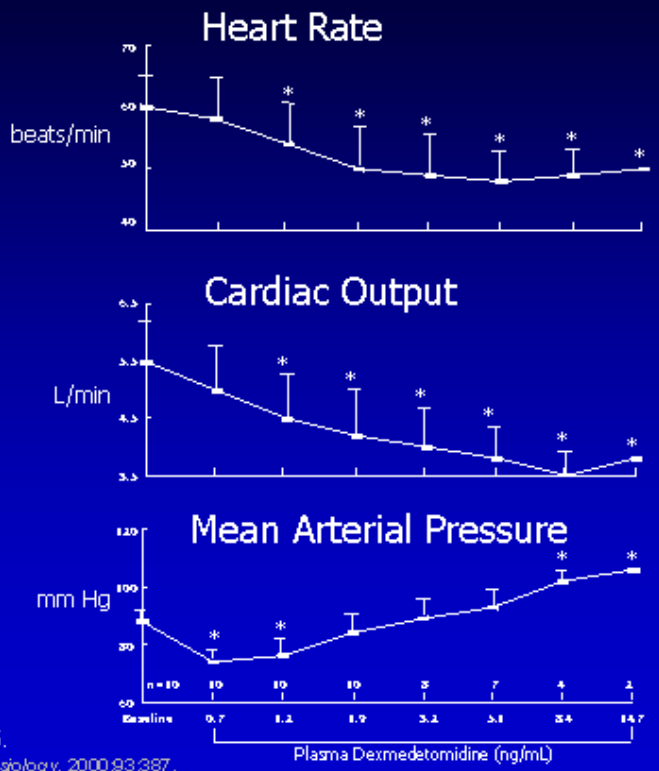
Central Cardiac Effects

- Hypotension
- Bradycardia
- Hypertension

Central Cardiac Effects

Hemodynamics

Maximum Tolerable Dose Study



*Significant change from preinfusion baseline, $P<0.05$.

Adapted from Ebert et al. *Anesthesiology*. 2000;93:387.

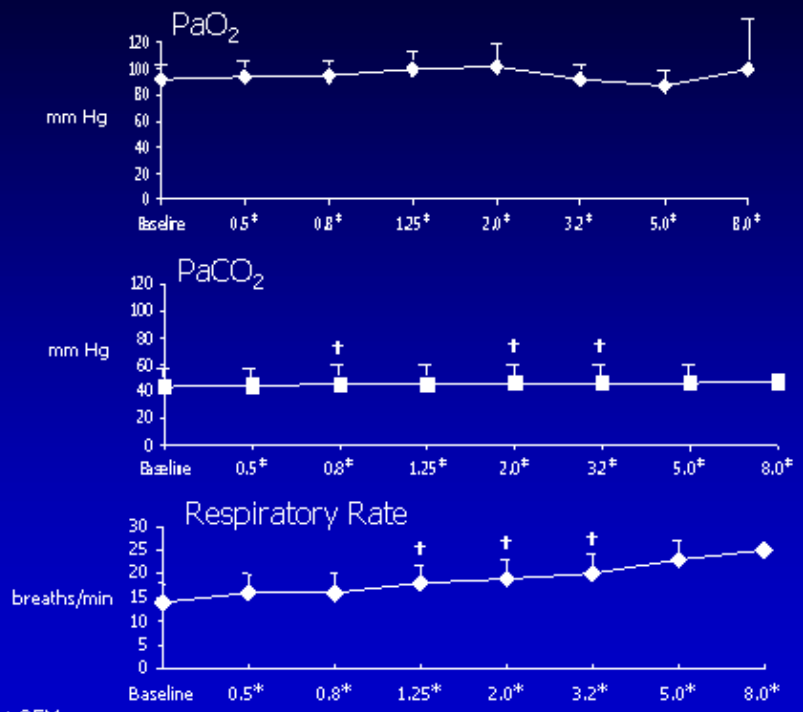
Central Respiratory Effects

- Bronchodilation
- Absence of Respiratory Depression
  - No potentiation of opioid-induced respiratory depression
  - Insignificant changes in RR, SpO2, pH, and PaCO2
    - *Venn et al. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care. 2000; 4:302-308*

Central Respiratory Effects

Respiratory Response

Maximum Tolerable Dose Study



Data are mean ± SEM.
*Target dexmedetomidine (ng/mL).
†P<0.05 compared with baseline values.
Adapted from Ebert et al. *Anesthesiology*. 2000;93:389.

Central Endocrine Effects

Decreased cortisol release (Adrenal Insufficiency?)

- Minimal depression demonstrated up to continuous 72 hour infusion.
- Continuous infusion for 7 days decreases cortisol release after ACTH by 40% (in animal model)

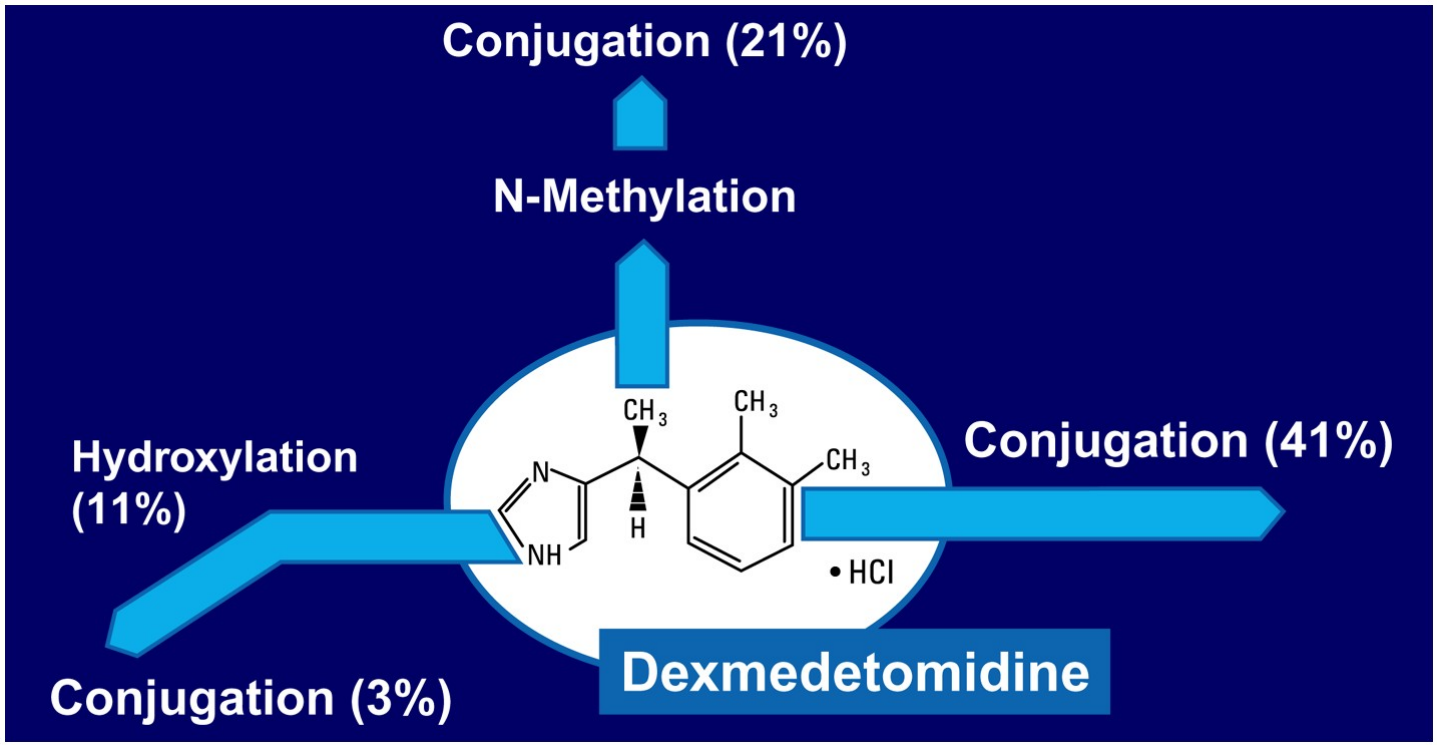
Peripheral Receptor Effects

- Arterial Vasocontriction
  - Due to direct alpha 2 activation at low doses
    - Occurs prior to vasodilation from inhibition of plasma catecholamine release.
  - Also due to cross reactivity with alpha 1 at higher doses (bolus)

- *Talke et al. Systemically administered Alpha2 agonist induced peripheral vasoconstirction in humans. Anesthesiology 2003; 99:65-70.*

Metabolism

- Metabolism
  - Biotransformation in liver by
    - Direct glucuronidation
    - CYP450



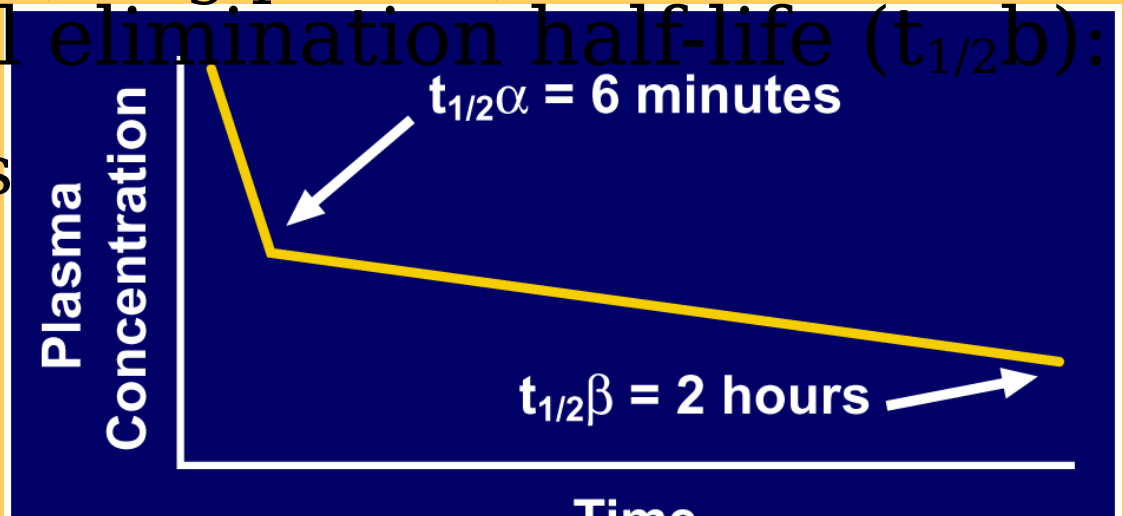
Elimination

- Elimination
  - 95% Urine
  - 4% Fecal
  - 1% Other

- *Dyck et al. Dexmedetomidine pharmacokinetics and pharmacodynamics. Anaesth Pharm Review. 1993; 1:238-245*

Pharmacokinetics

- Rapid distribution ($t_{1/2}a$):
  - 6 minutes
- Steady-state volume of distribution (Vss):
  - 118 liters
- Clearance:
  - 39 L/hr (70kg person)
- Terminal elimination half-life ($t_{1/2}b$):
  - 2 hours



Pharmacokinetics

- Pharmacokinetics were unchanged in severe renal impairment. Although a prolonged effect has been observed.
  - *Wolf et al. The pharmacokinetics of Dexmedetomidine in volunteers with sever renal impairment. Anesth Analg 2001; 93:1205-1209.*
- Protein Binding of 94%
  - Not displaced by any known medications to include fentanyl, lidocaine, warfarin, propranolol.

- *Dyck et al. Dexmedetomidine pharmacokinetics and pharmacodynamics. Anaesth Pharm Review. 1993; 1:238-245*

Dosing

- Supplied as 2cc vial containing 200mcg
  - To prepare, combine 2cc vial with 48cc NS (4mcg/cc)
  - Special Order, Cost $1500
- Loading Dose
  - 1 mcg/kg over 10 minutes
    - As alternative to loading dose, run 0.7 mcg/kg/hr for 26 minutes.
    - Bradycardia and hypertension observed
- Continuous infusion
  - 0.2 – 0.7 mcg/kg/hour
    - Linear kinetics
    - Studies limited to 24hrs

Side Effects

- Bradycardia and Hypertension
  - Usually limited to loading phase
- Hypotension
  - Secondary to decreased plasma Epi/NE
- Arrhythmia
  - Severe Sinus Brady and Cardiac Arrest
    - Reversible with antimuscarinics (Atropine)
    - *Weng et al. Dexmedetomidine and cardiac arrest. Anesthesiology 2004; 100:738-739.*
- Withdrawal has not been demonstrated

Side Effects

- Safety and Efficacy with children not established
- Safety and Efficacy in pregnancy not established. (Category C)
  - Animal studies indicate safety at two times human dose.
  - Likely secreted in breast milk. As medication is fully metabolized, neonatal effects are not anticipated.

Dexmedetomidine

- Clinical Uses
  - ICU
    - Phase III Trials
    - Improved Sleep Quality
    - Use in Withdrawal
  - Neuro
  - General OR
  - Cardiothoracic/Major Vascular
  - Regional
  - OB
  - Pain
  - Pediatrics

ICU

- Approved for continuous infusion in mechanically ventilated patients for 24 hours.
  - Based largely on two phase III trials.

ICU

- Present two Phase III trials that in part lead to approval in US for ICU sedation.
  - Its only approved indication
- Present beneficial effects in sleep quality in ICU ventilated patients.
- Present case report of novel use in treatment of withdrawal.

Phase III Trial

- *Martin et al. The role of the alpha 2 adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. J. Int Care Med. 18: 29-41, 2003*

- In double blind, randomized, placebo controlled, multicenter trial
- 401 post surgical patients were given dexmedetomidine or placebo.
  - 1mcg/kg load, 0.2-0.7mcg/kg/hr
- Primary endpoints of rescue propofol and morphine requirements.
- Secondary endpoints of RR, Sp02, HR, BP. duration of intubation, and nurse assessment.

Protocol

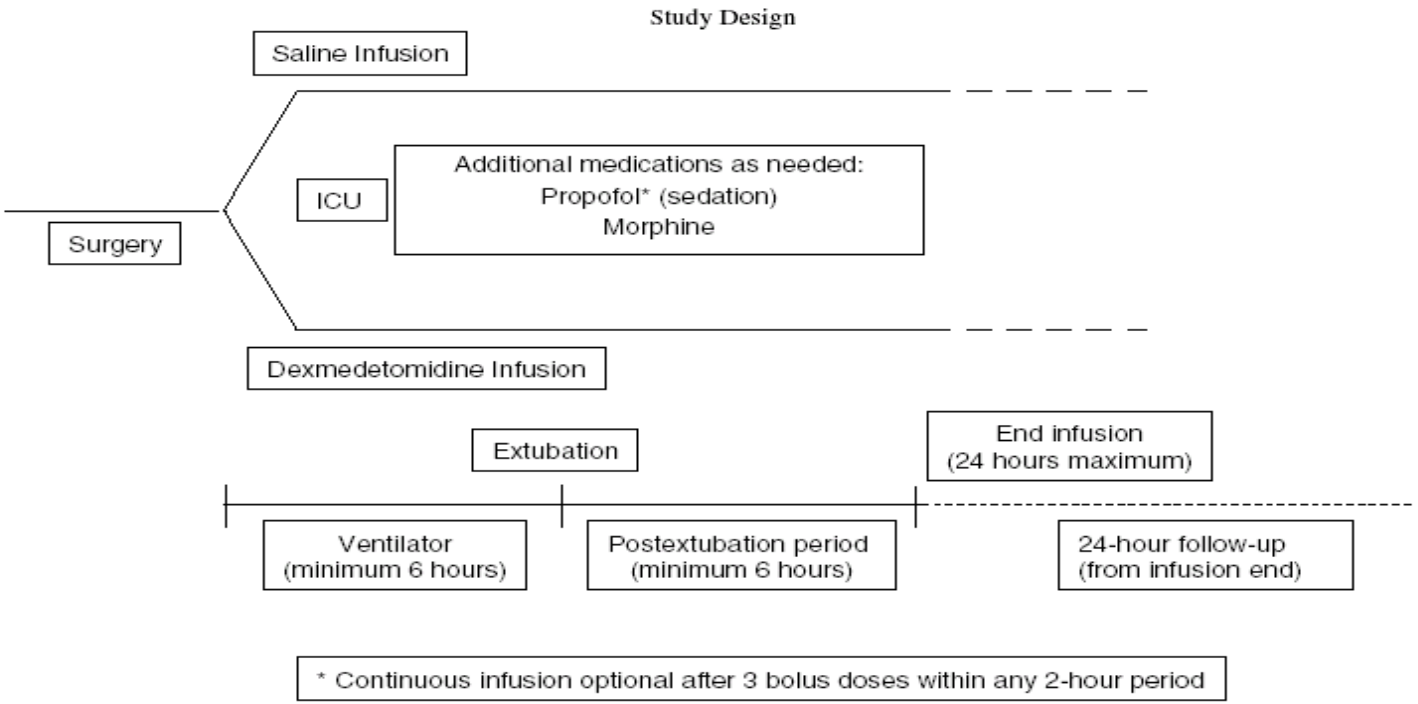


Fig 1. Study design. Study drug infusions began within 1 hour after the patients entered the intensive care unit (ICU) and continued uninterrupted for up to 24 hours. Study protocols required a minimum of 6 hours of assisted ventilation before extubation and a minimum of 6 hours with study drug administration after extubation.

Protocol

- Intraoperative management per anesthesiology discretion.
- Pt received Dexmedetomidine or Placebo upon ICU arrival.
  - Continued for 6 hours post extubation.
  - 1mcg/kg load, 0.2-0.7mcg/kg/hr
- After maximal infusion reached, Propofol and/or Morphine given per protocol.

Protocol

- Goal RSS of 3
  - Obtained with supplemental Propofol and/or Morphine after maximum Dexi

Table 1. Ramsay Sedation Scale

Score	Observation
1	Anxious, agitated, or restless
2	Cooperative, oriented, and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory stimulus
6	Asleep, no response

Propofol Requirements

- Decreases requirements for add on sedation.
  - Decreased requirements for Propofol
    - 81% patients required none or <50mg
      - Vs 41% in control
    - 86% less propofol use
      - In total mg delivered
    - (80 vs 560mg)
    - (5.3 vs 39.1mg/hr)

Morphine Requirement

- Decreases requirements for add on analgesia.
  - Decreased requirements for Morphine
    - 69% less morphine use
      - In total mg delivered
    - (1.31 vs 4.1mg)
    - (0.14 vs 0.50mg/hr)

Times to Extubation

- Similar between groups
  - Partly due to protocol requiring minimum intubation time of six hours.
    - No improvement with dexmedetomidine

Respiratory Variables

- No change in RR, Sp02, PaCO2

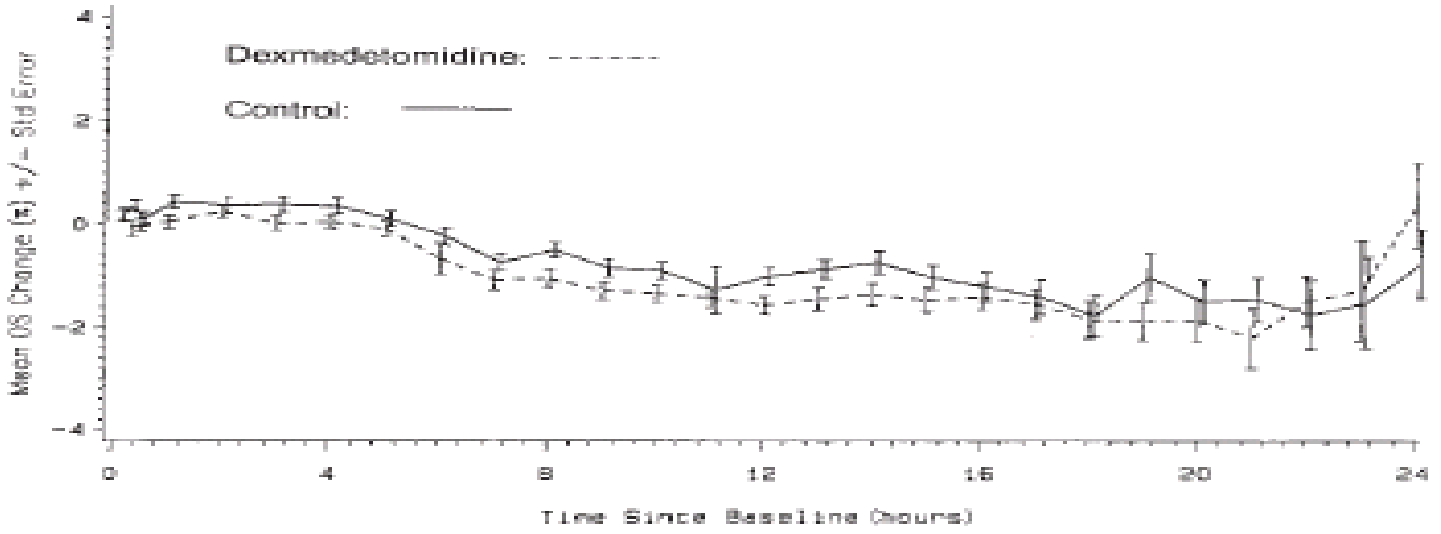


Fig 2. Mean change from baseline for oxygen saturation while receiving study drug. Control group values are offset +6 minutes for comparison of standard error bars. Baseline in the dexmedetomidine group was 98.7% and in the control group was 98.5%.

Hemodynamics

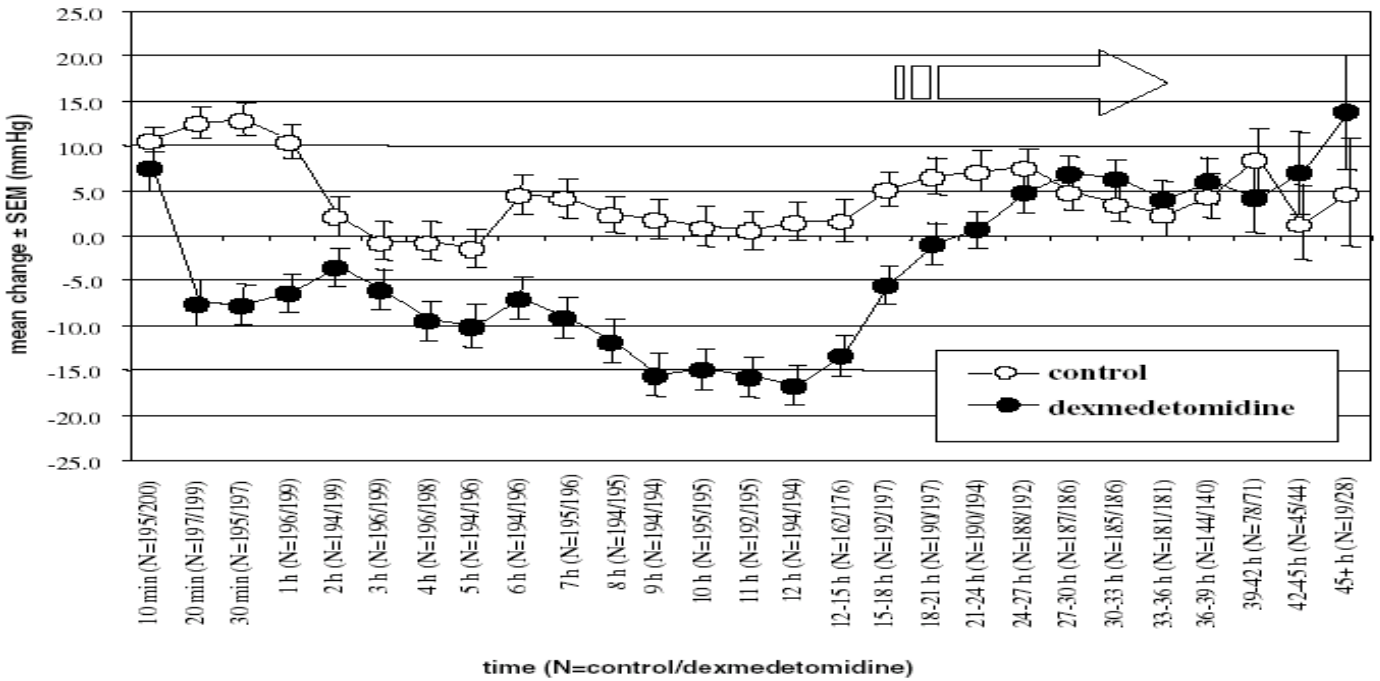


Fig 3. Mean change from baseline in systolic blood pressure during the entire study period. This figure includes all randomized intent-to-treat patients, whether still receiving study drug or not. N equals the number of control/dexmedetomidine patients with data available at each time point. Study drug was stopped after 12 hours for most patients (large dashed arrow). Vital signs were collected at 3-hour intervals for another 24 hours after study drug infusions were stopped. By hour 16, study drug had been stopped for approximately two thirds of the patients in both groups.

Hemodynamics

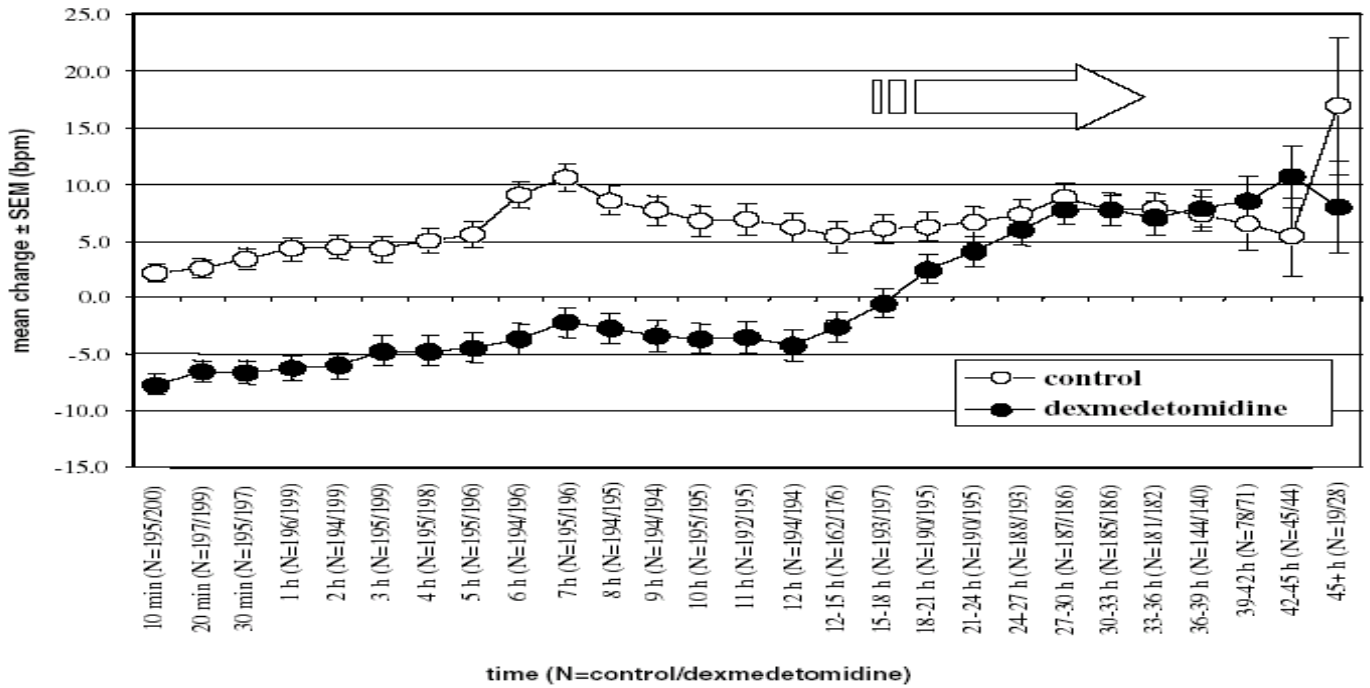


Fig 4. Mean change from baseline in heart rate for all patients during and after study drug. This figure includes all patients for 48 hours after the start of study drug (same population as in Fig 3). The large dashed arrow begins at the point where study protocol minimums were fulfilled. After 12 hours, study drug had been stopped for most patients. Baseline mean heart rate in the dexmedetomidine group was 80.8 bpm and in the control group was 79.8 bpm. N equals the number of placebo/dexmedetomidine patients whose data were included at each time point.

Adverse Events

Table 6. Most Common Treatment-Emergent Adverse Events

All Treated Patients	Dexmedetomidine (n = 203)	Control (n = 198)	*P* Value
Patients with at least 1 treatment-emergent adverse event	121 (60%)	112 (57%)	.545
Hypotension	61 (30%)	20 (10%)	< .001
Hypertension	24 (12%)	45 (23%)	.005
Nausea	22 (11%)	19 (10%)	.743
Bradycardia	18 (9%)	4 (2%)	.003
Vomiting	10 (5%)	11 (6%)	.826
Hypoxia	8 (4%)	5 (3%)	.575
Mouth dry	7 (3%)	1 (< 1%)	.068
Fever	6 (3%)	7 (4%)	.785
Tachycardia	4 (2%)	6 (3%)	.539
Hemorrhage	3 (1%)	7 (4%)	.216
Atrial fibrillation	3 (1%)	5 (3%)	.499
Acidosis	3 (1%)	5 (3%)	.499
Confusion	3 (1%)	6 (3%)	.333
Agitation	2 (< 1%)	6 (3%)	.171
Atelectasis	1 (< 1%)	9 (5%)	.010
Rigors	1 (< 1%)	8 (4%)	.019

Adverse events experienced by ≥ 3% of patients in either group. *P* values were calculated by Fisher's Exact Test. Terms are from World Health Organization-Adverse Reaction Terms.

Phase III Trial

- *Venn et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit.*

- In double blind, randomized, placebo controlled trial
- 119 post surgical patients were given Dexmedetomidine or Placebo.
- Primary endpoints of rescue midazolam and morphine requirements.
- Secondary endpoints of RR, Sp02, and duration of intubation, HR, BP.

Protocol

- Intraoperative management per anesthesiology discretion.
- Pt received Dexmedetomidine or Placebo upon ICU arrival. Continued for 6 hours post extubation.
  - 1mcg/kg load, 0.2-0.7mcg/kg/hr
- After maximal infusion reached, midazolam and/or Morphine given per protocol.

Protocol

- Goal RSS of 2

Table 1. Ramsay Sedation Scale

Score	Observation
1	Anxious, agitated, or restless
2	Cooperative, oriented, and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory stimulus
6	Asleep, no response

Midazolam Requirements

- Decreases requirements for add on sedation.
  - Decreased requirements for Midazolam
    - Six times more midazolam use in control

	Dexmedetomidine ($n=47$)	Placebo ($n=51$)	p-value
Midazolam			
0–6h ($\mu g.kg^{-1}$)	4.3 (5.8)	$18.5\ (24.6)\times10^{-3}$	<0.0001
whilst intubated ($\mu g.kg^{-1}.h^{-1}$)	4.9 (5.8)	$23.7\ (27.5)\times10^{-3}$	<0.0001

Morphine Requirement

- Decreases requirements for add on analgesia.
  - Decreased requirements for Morphine
    - Reduced use by half

Morphine			
0–6h ($\mu g.kg^{-1}$)	9.1 (9.6)	$15.3\ (17.4) \times 10^{-3}$	0.0135
whilst intubated ($\mu g.kg^{-1}.h^{-1}$)	11.2 (13.4)	$21.5\ (19.4) \times 10^{-3}$	0.0006
whilst extubated ($\mu g.kg^{-1}.h^{-1}$)	4.8 (11.0)	$5.8\ (5.5) \times 10^{-3}$	0.027
observation period ($\mu g.kg^{-1}.h^{-1}$)	5.6 (10.6)	$9.7\ (17.7) \times 10^{-3}$	ns

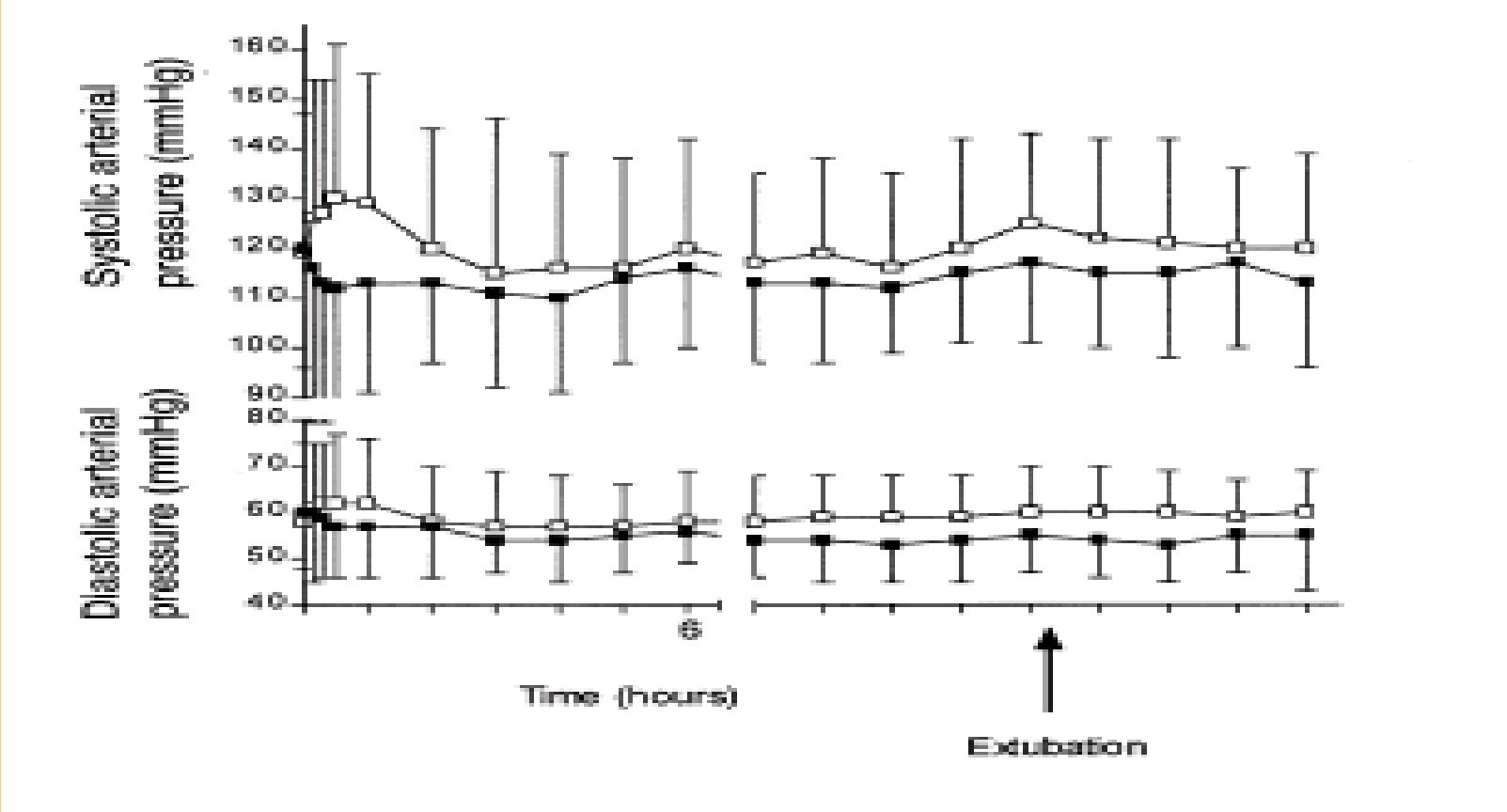
Times to Extubation

- Similar between groups
  - Partly due to protocol requiring minimum intubation time of six hours.
    - No improvement with dexmedetomidine

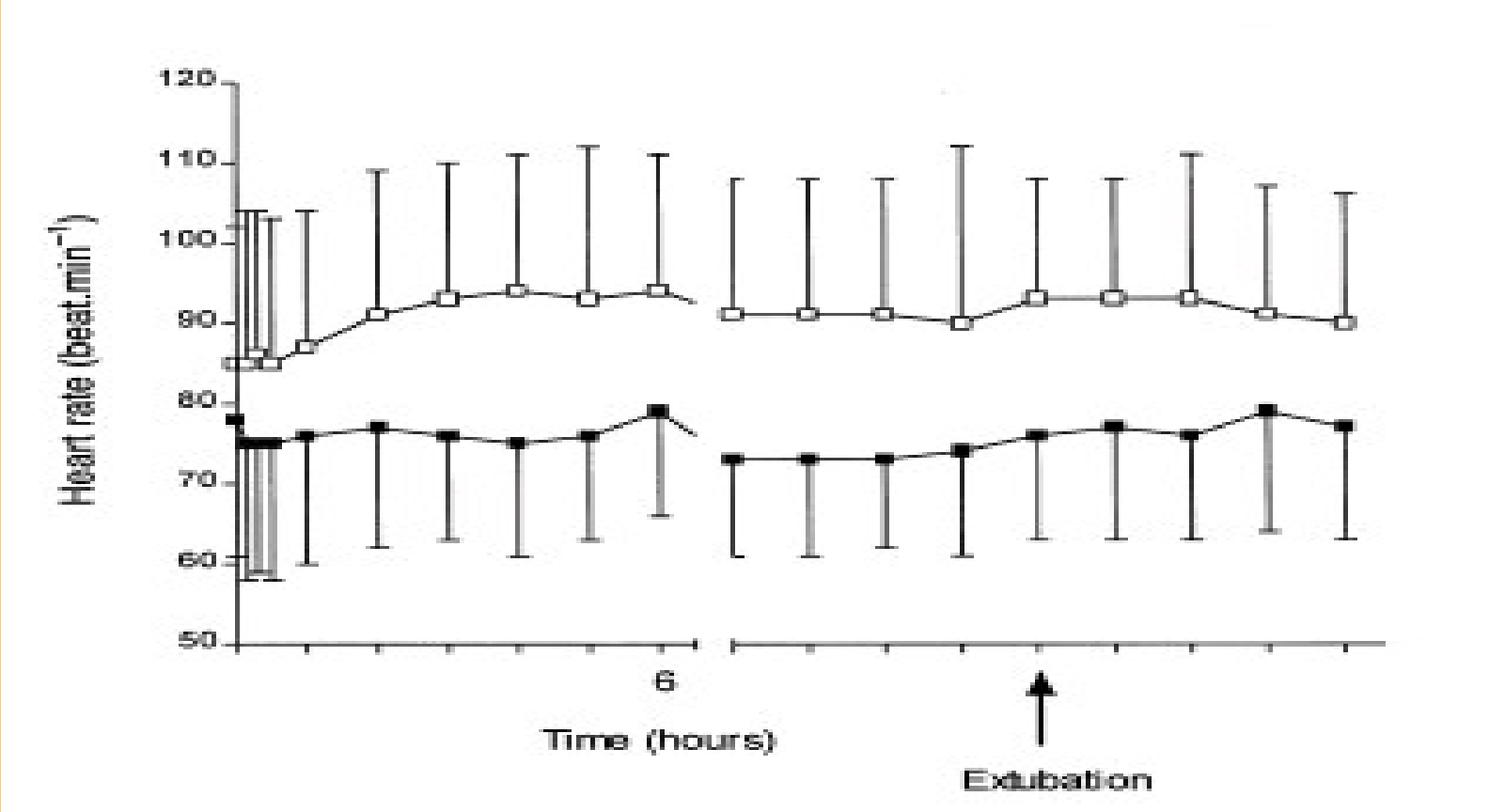
Respiratory Variables

- No change in RR, Sp02

Hemodynamics



Hemodynamics



Characteristics of an ideal sedation agents for the ICU

- Lack of respiratory depression
- Analgesia
- Highly titratable
  - Due to short elimination half-life
- Sedation
  - Maintenace of orientation and arousability
- Anxiolytic
- Amnesia
- Hemodynamic stability

Sleep in the ICU

- Identify the problem
  - lack of quality and quantity of sleep
- ICU patients typically obtain less than 2 hours of sleep per 24 hours.
  - *Cooper et al. Sleep in critical ill patients requiring mechanical ventilation. Chest 2000; 117: 809-818*
- Sleep deprivation has been associated with delirium and psychotic reactions in 60-80% of ventilated ICU patients.
  - *Ely et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004; 291: 1753-1762*

Mimics Natural Sleep

- CBF studies indicate that dexmedetomidine induced no significant difference in the blood flow signal compared to that of natural sleep.
- These same studies indicate benzodiazepines produce different CBF patterns from that of natural sleep.
  - *Coull et al. Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. Neuroimage 2004: 22:315-322*

Mimics Natural Sleep

- Dexmedetomidine sedation may induce reparative and restorative functions similar to that seen in natural sleep.
  - *Nelson et al. The alpha2 agonist dexmedetomidine converges on an endogenous sleep promoting pathway to exert its sedative effects. Anesthesiology. 2003; 98:428-436*

Adjunct in Withdrawal

- Case Report of 33 yo patient in ICU who received haloperidol, plus lorazepam and fentanyl gtt for 25 days. Pt extubation was delayed secondary to withdrawal.
- Dexmedetomidine was administered over 7 days. Pt extubated on day 5. On day 7, he was off all sedatives without evidence of withdrawal. Hemodynamic stability was maintained throughout.
  - *Multz. Prolonged dexmedetomidine infusion as an adjunct in treating sedation induced withdrawal. Anesth Analg. 2003;96:1054-1055*

Summary

- Safe alternative to standard sedative and analgesics
  - Few Adverse Events
- Sedation and Analgesia Demonstrated
  - Permits lower doses of Propofol, Morphine, and Midazolam
    - Dexmedetomidine is an incomplete sedative analgesic
- Unique sedative that allows arousability during deep sedation, with moderate amnesia

Summary

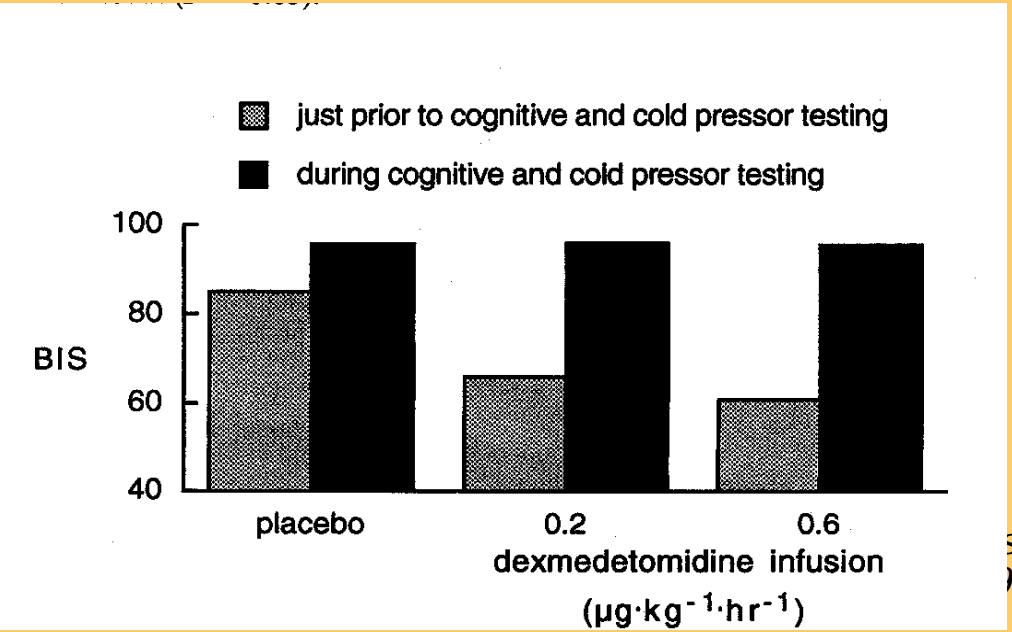
- Improves quality and quantity of sleep
  - mimic natural sleep
- Beneficial in withdrawal
- Infusion may be continued before,during, and after extubation.
- No clear advantage over standard ICU medications.

Dexmedetomidine

- Clinical Uses
  - ICU
  - Neuro
    - Unique Sedation Properties
    - Awake Craniotomy
    - Awake Carotid Endarterectomy
  - General OR
  - Cardiothoracic/Major Vascular
  - Regional
  - OB
  - Pain
  - Pediatrics

Arousal Response for Deep Sedation

- Patients maintained ability to interact while sedated
  - Eluded to in Phase III trials
  - Quantified here with relation to BIS



- *Hall et* *small-dose de* *99-705.*

Awake Craniotomy

- Case report of craniotomy with intraoperative brain mapping of the cortical speech area during tumor resection
  - Sole agent for maintenance phase
  - Arousable and cooperative from deep sedation (BIS 60-75)
    - BIS 95 at 0.1mcg/kg/hour
    - Minimal recall
  - Verbal with native airway
    - PaCO2 of 42, PaO2 of 156

      - *Bekker et al. The use of dexmedetomidine infusion for awake craniotomy. Anesth Analg. 2001;92:1251-1253.*

Awake Craniotomy

- Chart review of 10 patients who received anesthetic by 4 anesthesiologists. Five cases were MAC, while five were asleep-awake-asleep.
- After being aroused from deep sleep by voice command, patients were required to perform complex neurologic tasks to include motor and sensory, naming, reading, verbal, writing, and counting.
- Load (0.5-1mcg/kg) given over 20minutes, followed by infusion of 0.01-1.0mcg/kg/hr.

- *Mack et al. Dexmedetomidine and neurocognitive testing in awake craniotomy. J Neurosurg Anesth. 2004;16:20-25*

Awake Carotid Endarterectomy

- A randomized double blind placebo controlled study of 66 patients is reviewed.
  - *Bekker et al. Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects. J Neurosurg Anesthesiol 2004; 16:126-135.*
- Primary endpoint adequate sedation per OAA/S Score.

TABLE 1. Intraoperative Assessment of Sedation Level

Treatment	Number of Times Patients Achieved an OAA/S Score of 4					
	0/4	1/4	2/4	3/4	4/4	Total
Control, n	4	14	7	6	0	31
%	12.9	45.2	22.6	19.4	0.0	
Dexmedetomidine, n	1	6	11	10	3	31
%	3.2	19.4	35.5	32.3	9.7	
Total	5	20	18	16	3	62

Chi-square for the primary end point was 9.89; $P = 0.04$.
OAA/S, Observer's Assessment of Alertness-Sedation.

Awake Carotid Endarterectomy

- Secondary endpoints
  - Avoidance of Postoperative Hypertension with reduced plasma Epi and NE levels
    - A trend toward prevention of perioperative ischemia (ECG changes)
  - Increased intraoperative shunt placement
    - Due to approx 10% lower intraopertive blood pressures? Although all maintained within predetermined levels with vasoconstrictor use

TABLE 4. Perioperative Complications in the Dexmedetomidine and Control Groups

Complication	Dexmedetomidine		Control	
	# of Patients (n = 31)	% of Patients	# of Patients (n = 31)	% of Patients
Intra-arterial shunt	2	6	6	19
Postoperative ECG changes	5	16	9	29
Stroke	1	3	0	0
Myocardial infarction	0	0	1	3
Conversion to general anesthesia	1	3	1	3
Back to OR	1	3	1	3

Complications were compared using chi-square/Fisher exact test. $P < 0.05$ was considered statistically significant. No significant differences were found among the groups.

Neuroanesthesia-SSEP

- Case Report
  - Experience with cervical fusion indicate insignificant differences in amplitude and latency vs propofol.
    - *Bloom et al. Dexmedetomidine infusion and somatosensery evoked potentials. J Neurosurg Anesth. 2001;4:320-322.*
- Animal model indicates that SSEP monitoring is preserved or even improved
  - Dexmedetomidine may have an intrinsic ability to improve SSEP signal.
    - *Li et al. Preservation of the cortical somatosensory-evoked potential during dexmedetomidine infusion in rats. Anesth Analg. 2003;96:1155-1160.*

Summary

- Ideally suited when patient must remain interactive during an anesthetic
  - Anxiolytic
  - Sedative
    - With unusual ability to avoid confusion
  - Amnestic
  - Analgesic
  - No respiratory depression
    - avoidance hypercapnia
- Preserved or Improved SSEP signal

Dexmedetomidine

- Clinical Uses
  - ICU
  - Neuro
  - General OR
    - Anesthetic Sparing
    - Analgesic Sparing
    - Amnestic
    - Difficult Airway
      - FOB
      - TIVA (GAWAC)
    - Anti-Shivering
  - Cardiothoracic/Major Vascular
  - Regional
  - OB
  - Pain
  - Pediatrics

Anesthetic Sparing Properties

- Dexmedetomidine decreases Isoflurane requirements in a dose dependent manner. High dose dexmedetomidine will decrease MAC to 0.5%. Pharmacokinetics are unchanged by Isoflurane.
  - *Khan et al. Effects of dexmedetomidine on Isoflurane requirements in healthy volunteers. Brit J Anesth 1999; 83:372-380.*
  - *Aantaa et al. Dexmedetomidine … reduces anesthetic requirements for patients undergoing minor gynecologic surgery. Anesthesiology. 1990; 73:230-235.*
- N2O and Dexmedetomidine produce an additive analgisic effect at the level of the spinal cord. Dexmedetomidine anatagonizes N2O induced increase in neural activity at the level of the locus ceruleus, thus providing enhanced and more durable analgesia than N2O alone.
  - *Dawson et al. Dexmedetomidine enhances analgesic action of Nitrous Oxide. Anesthesiology 2004; 100: 894-904.*

Analgesic Sparing Properties

- Incomplete analgesia of Dexmedetomidine was already shown in Phase III trials as reduced, but not eliminated, requirements for Morphine.
- This reduction in Morphine requirements has been reproduced in post surgical patients. 34 patients receiving major surgery received Dexmedetomidine prior to PACU admission and for 4 hours afterward.
  - 65% of Dexmedetomidine patients required no additional Morphine in PACU and total Morphine requirements were 66% less. Analgesic effect of Dexmedetomidine quickly diminished after halting the infusion, as total Morphine use for all patients was the same after 24hrs.
  - *Arain et al. The efficacy of Dexmedetomidine vs. Morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 2004; 98:153-158.*

Amnestic Properties

- While unique property of a sedated patient who is arousable without confusion has already been mentioned. However, the amnestic quality of Dexmedetomidine is quantified below.
- Seven volunteer patients received variable doses of Dexmedetomidine and their ability to recall words was tested.
  - Any dose of Dexmedetomidine was associated with a 50% impairment of memory.
  - *Hall et al. Sedative, amnestic, and analgesic properties of small-dose Dexmedetomidine infusions. Anesth Analg 2000; 90: 699-705.*

Difficult Airway-FOB

- Management of the difficult airway usually includes airway topicalization with sedation. Problems with this technique include time consuming nerve blocks and respiratory depression from sedatives.
- As an alternative to standard airway management. The use of Dexmedetomidine allows management of the airway without respiratory depression and potentially without FOB or selective nerve blocks.
- Two Case Reports are presented. Dexmedetomidine was chosen for its respiratory, analgesic, amnestic, and antisialgogue properties.

Difficult Airway-FOB

- Case Report of patient with known difficult airway with multiple failed intubations. This was combined with Ketamine to counteract the hypotension and bradycardia sometimes observed with Dexmedetomidine.
  - Successful FOB was performed without ventilatory compromise on room air and without recall. Selective nerve blocks were used.
  - *Scher et al. Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fiberoptic intubation. Can J Anesth 2003; 50: 607-610.*
- Another Case Report demonstrated the utility of Dexmedetomidine in the management of three patients with difficult airway. Standard Dexmedetomidine load and infusions were used without selective nerve blocks.
  - *Grant et al. Dexmedetomidine infusion for sedation during fiberoptic intubation: a report of three cases. J Clin Anesth 2004; 16: 124-126.*

Difficult Airway-TIVA

- Case Report where Dexmedetomidine was used as the sole agent for anesthesia and the management of the difficult airway.
- 3 patients in which airway instrumentation was not possible or desirable (severe subglottic stenosis, severe emphysema with recent ICU admission for respiratory failure, and patient with artificial trachea).

Difficult Airway-TIVA

- These patients received Dexmedetomidine load plus infusion 0.7mcg/kg/hr. Infusion was increased as high as 10mcg/kg/hr to maintain anesthetic depth for the duration of surgery (usually less than one hour).
  - Dexmedetomidine was the sole anesthetic used.
  - All patient discharged from PACU within 2 hours.
- This anesthetic permitted patients to maintain spontaneous ventilations on room air for the entire procedure. In addition, one patient tolerated direct laryngoscopy during the procedure.
  - *Ramsey et al. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology 2004; 101: 787-790.*

PACU-Shivering

- Hypothermia is a common occurance in post surgical patients. Occasionally this hypotension is induced purposefully, such as for neuroprotection or DHCA. Unfortunately hypothermia is associated with adverse affects to include shivering (discomfort, increased oxygen consumption), vasoconstriction, coagulopathy, and sympathetic nervous system activation.
- Currently Meperidine is used to counteract shivering, although it has no effects on the other components of hypothermia.

PACU-Shivering

- Dexmedetomidine may offer advantages in addition to it's antishivering actions, especially limiting sympathetic nervous system activation.
- 10 volunteer patients were subjected to variable depths of hypothermia and medical treatment. Meperidine and Dexmedetomidine were administered on separate days to achieve target plasma concentrations. The shivering threshold was determined as oxygen consumption greater than 25% of baseline.
  - Control shivering threshold was 36.7C
  - Dexmedetomidine lowers threshold to 36.0C
  - Meperidine lowers shivering threshold to 35.5C.
  - The combination was additive, lowering the threshold to 34.7C.

  - *Doufas et al. Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. Stroke. 2003; 34: 1218-1223.*

PACU-Shivering

- In another study, the efficacy of Dexmedetomidine in prevention of shivering was demonstrated as a secondary endpoint. It was shown that Dexmedetomidine decreased postoperative shivering 10-fold.
  - *Aho et al. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. Anesth Analg 1991; 73:112-118.*
- Efficacy of other alpha2 agonists (Clonidine) have also been demonstrated.
  - *Kranke et al. Single dose parenteral pharmacological interventions for the prevention of postoperative shivering: A quantitative systematic review of randomized controlled trials. Anesth Analg 2004; 99:718-727.*
  - *Kranke et al. Pharmacological treatment of postoperative shivering: A quantitative systematic review of randomized controlled trials. Anesth Analg 2002; 94:453-460.*

Summary

- Useful Adjunct to a standard anesthetic
  - Anesthetic, Analgesic, and Amnestic Properties
- Limits adverse effects of postoperative hypothermia
  - Lowers Shivering Threshold
  - SNS Activation
- May be used as sole anesthestic
- Useful in Management of Difficult Airway
  - Avoidance of selective nerve blocks
  - May permit Direct Larynoscopy in spontaneously ventilating patient

Dexmedetomidine

- Clinical Uses
  - ICU
  - Neuro
  - General OR
  - Cardiothoracic/Major Vascular
    - Reduction in Perioperative Ischemia/Cardiac Death
    - Alternative to B-Blockade
    - CABG
  - Regional
  - OB
  - Pain
  - Pediatrics

Reduces Ischemia and Death

- Initial experience with alpha2 agonists, Clonidine and Mivazerol, indicates that they offer similar protection to that of B-blockade
- In patients undergoing vascular surgery, alpha2 agonists have demonstrated reduction in perioperative infarction and cardiac death. A 50% reduction in perioperative mortality has been demonstrated in all types of surgical patients. This reduction is similar to that of B-blockade.
  - *Oliver et al. Effect of Mivazerol on perioperative cardiac complications during noncardiac surgery in patients with coronary heart disease. Anesthesiology. 1999:91:951-961.*
  - *Europe Research Group. Perioperative sympatholysis: Beneficial effects of the alpha2 adrenoceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. Anesthesiology 1997;86:346-363.*
  - *Goldman et al. Evidence based perioperative risk reduction. Am J Med. 2003;114:763-764*

Reduces Ischemia and Death

- With the alpha2 agonist, Clonidine, a double blind placebo controlled trial and two meta analysis' found a reduction of perioperative ischemia and cardiac death. This reduction was similar between B-blockade and Clonidine.
  - *Stevens et al. Pharmacologic myocardial protection in patients undergoing noncardiac surgery: A Quantitative Systematic Review. Anesth Analg 2003;97:623-633.*
  - *Nishina et al. Efficacy of Clonidine for prevention of perioperative myocardial ischemia: A critical appraisal and meta-analysis of the literature. Anesthesiology 2002;96:323-329.*
  - *Wallace et al. Effect of Clonidine on Cardiovascular Morbidity and Mortality after Noncardiac Surgery. Anesthesiology 2004;101:284-293.*
- ***These finding have not been confirmed with dexmedetomidine!***

Alternative to B-Blockade

- While alpha2 agonists and B-blockade offer similar advantages in reduction in ischemia, infarction, and cardiac death, alpha 2 agonists offer the advantage of fewer contraindications.
- Alpha2 agonists are preferable in patients with hyper-reactive airway disease, AV block, or left ventricular dysfunction.
- A case report demonstrates its usefulness in a patient with LV dysfunction and tachycardia in whom B-blockade is relatively contraindicated.
  - *Ruesch et al. Treatment of persistent tachycardia with Dexmedetomidine during off-pump cardiac surgery. Anesth Analg. 2002;95:316-318.*
- While B-blockade may induce bronchospasm, Dexmedetomidine actually reduces it.
  - *Groeben et al. Effects of the alpha2 agonist dexmedetomidine on bronchoconstriction in dogs. Anesthesiology 2004;100:359-363.*

CABG

- Usefulness in Cardiac Surgery is limited to post-operative weaning and extubation.
- As previously stated in the Phase III trials, Dexmedetomidine offers the following advantages:
  - reduction in sedative and analgesic requirements, cooperative patient, lack of respiratory depression and hemodynamic stability
- An additional study limited to CABG patients demonstrated the above findings with the additional benefit of reduced B-blockade, Epi, Diuretic, and antiemetic use.
  - *Herr et al. ICU sedation after coronary bypass graft surgery: Dexmedetomidine based vs. propofol based sedation regimens. J Card Vasc Anesth 2003; 17:576-584.*

Summary

- Alternative to B-blockade
  - Similar reduction in ischemia, infarction, and cardiac death
- Preferable when B-blockade is contraindicated
  - Pulmonary Disease,LV dysfunction, AVB
- CABG patients benefit from lower HR, BP, plasma catecholamines, and diuresis.

Dexmedetomidine

- Clinical Uses
  - ICU
  - Neuro
  - General OR
  - Cardiothoracic/Major Vascular
  - Regional
    - Intravenous Regional Anesthesia
  - OB
  - Pain
  - Pediatrics

Past Experience

- The utility of the alpha2 agonist, Clonidine, has been well documented. It has proven useful in IVRA, Epidural, Spinal, and Nerve blocks. It can provide analgesia either as a sole agent or in combination with local anesthetics.
  - *Eisenach et al. Alpha2 adrenergic agonists for regional anesthesia. Anesthesiology 1996; 85:655-674.*
  - *Gabriel et al. Alpha2 agonists in regional anesthesia and analgesia. Curr Opin Anesth 2001; 14:751-753*
- With the exception of IVRA, use of Dexmedetomidine has not been reported in Regional Anesthesia

Intravenous Regional Anesthesia

- 30 patients undergoing hand surgery by “Bier Block” received 40cc 0.5% lidocaine with or without 0.5mcg/kg Dexmedetomidine.
- Primary endpoints included onset time, duration of block, time to tourniquet pain, time to first analgesic, and total analgesic use.

Intravenous Regional Anesthesia

- Patients with Dexmedetomidine experienced shortened onset, prolonged duration, improved tolerance for the tourniquet, while maintaining improved VAS scores.

Table 1. Onset and Recovery Times of Sensory and Motor Block, Initial Time of Tourniquet Pain, the Duration of Analgesia, and the Amount of Intraoperative and Postoperative Analgesic

	Group L	Group LD
Sensory block onset time (min)	7 ± 2*	5 ± 2
Sensory block recovery time (min)	4 ± 1†	7 ± 3
Complete motor block onset time (min)	15 ± 3*	10 ± 4
Complete motor block recovery time (min)	5 ± 1†	8 ± 3
Initial time of tourniquet pain (min)	32 ± 10†	53 ± 10
The amount of intraoperative analgesic (fentanyl micrograms)	60 ± 12†	31 ± 31
The duration of analgesia postoperative (min)	129 ± 54*	564 ± 644
The amount of postoperative analgesic (diclofenac milligrams)	119 ± 28†	55 ± 45

upon release.

- Patients were provided with improved intraoperative anesthesia and prolonged postoperative analgesia.

Summary

- Role of Clonidine as an adjunct in regional anesthesia is well established.
- Role of Dexmedetomidine is less clear.

Dexmedetomidine

- Clinical Uses
  - ICU
  - Neuro
  - General OR
  - Cardiothoracic/Major Vascular
  - Regional
  - OB
  - Pain
  - Pediatrics

Pediatrics

- Only one study has been published to show use in children.
  - Found to be useful to decrease PACU agitation after short Sevoflurane based anesthetic.
  - *Ibacache et al. Single-dose Dexmedetomidine reduces agitation after sevoflurane anesthesia in children. Anesth Analg 2004; 98:60-63.*
- Safety has not been demonstrated in the pediatric population.

OB

- As with regional anesthesia, Clonidine has been used in epidural and spinal anesthesia for the pregnant patient.
- The use of Dexmedetomidine in this setting has not been studied.
- In addition, safety has not been demonstrated in pregnancy or in breast feeding mothers. (Category C)

Pain

- The role of alpha2 agonist is the management of chronic pain has only recently been investigated. It has not yet gained widespread use in this regard.
- There are no published studies showing the use of dexmedetomidine in the management of chronic pain.
- A few studies show Clonidine to be useful in management of SMP

Pain

- A few studies show Clonidine to be useful in management of
  - SMP
    - *Reuben et al. Intravenous regional Clonidine in the management of sympathetically maintained pain. Anesthesiology 1998; 89:527-530.*
  - CRPS
    - *Reuben. Preventing the development of Complex Regional Pain Syndrome after surgery. Anesthesiology 2004; 101:125-1224.*

Summary

- Highly titratable
- Sedation, anxiolysis, analgesia, amnesia
- Minimal respiratory depression
- Mimics natural sleep while permitting arousal
- Decreases anesthetic requirements
- Predictable and Stable HD Changes
  - Attenuates hypertension and tachycardia
- Decreases shivering
- Patients are uniquely arousable and responsive
- Role in the management of the difficult airway and for TIVA is especially promising

Summary

- ICU
  - Alternative to standard sedation protocol
  - Uniquely useful in withdrawal
  - May more closely mimic natural sleep
- Neuro
  - Especially useful for awake craniotomy and carotid endarerectomy
  - Unique state of cooperative arousal
- Gen OR
  - Especially beneficial in difficult airway
  - Beneficial antiemetic and antishivering properties
- Cardiothoracic/Major Vascular
  - Usefulness in CAD similar to that of B-blockade with fewer contranindications
- Regional, OB, Peds, Pain
  - Usefulness currently limited